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ARTICLE

The safety of commonly used vitamins and minerals

SUMMARY

Dietary supplements are the most common type of complementary medicine in Australia, reportedly used by 47% of the population. Vitamins and minerals are particularly popular.

Like all medicines, supplements can cause potential harms such as adverse reactions, drug interactions, monetary cost, delay of more effective therapy, false hope, and increased medication burden.

Although most vitamins and minerals are available for open sale, many are subject to legal restrictions as scheduled medicines, depending on the dose.

Consumers are at risk of overdose when the same ingredient is present in multiple products.

Health professionals can assist consumers by discussing the potential benefits and harms of vitamins and minerals and assisting them to find authoritative information.

Adverse events with vitamins and minerals should be reported to the Therapeutic Goods Administration.

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Introduction

Dietary supplements are natural health products used to supplement the diet, such as vitamins, minerals, amino acids, enzymes, plant extracts, algae and macroscopic fungi.[1] Although these products are more commonly referred to as complementary medicines in Australia, particularly for regulatory purposes by the Therapeutic Goods Administration (TGA), the term dietary supplement is frequently used by consumers whose intention is to augment their diet rather than treat disease.

Dietary supplements dominate the complementary medicines industry in Australia. Sales reached AU$5.6 billion in 2019 after having more than doubled over the preceding 10 years.[2] Complementary medicines are in widespread use in Australia, with a recent national survey showing 63% of people use them regularly. Dietary supplements containing vitamins and minerals were the most popular type of complementary medicine and were reportedly used by 47% of respondents.[3]

Potential harms of vitamins and minerals

One reason for the persistent popularity of vitamins and minerals is the perception that they are harmless. There are many potential harms (see Box 1 for potential adverse effects of commonly used vitamins and minerals) but, unlike conventional medicines, manufacturers of vitamins and minerals are not required to submit extensive documentation about safety or effectiveness of their products in order to be included in the Australian Register of Therapeutic Goods.

It is wise to remember that there are several different types of harm that can occur with any medicine other than just adverse drug reactions. See Box 2 for the six potential harms which may be a helpful guide to risk assessment.[4]

Marketing of vitamins and minerals is generally based on their claimed benefits with little, if any, mention of their potential harms. Consumer information leaflets are not provided, and few dietary supplements carry warnings of potential adverse effects on their packaging. Nonetheless, there are well-recognised harms from the ingredients of dietary supplements, especially when taken in high doses. For example, higher dose products of vitamin A and selenium are regulated as Schedule 2, 3 and 4 medicines because of their documented toxicity.

Vitamins and minerals are generally used safely when prescribed in medical settings for the treatment or prevention of deficiency states and other appropriate conditions. For example, vitamin B_3 is used for hyperlipidaemias and folic acid is used in pregnancy to prevent birth defects (e.g. anencephaly, spina bifida). The key to the safety of vitamins and minerals is the prescribed dose, which is usually derived from research demonstrating that the benefits outweigh the harms. This is often not the case when consumers are self-medicating with products purchased on the open market, as consideration is rarely given to the

Box 1 Potential adverse effects of commonly used vitamins and minerals

Vitamin A/retinol

Acute toxicity associated with ingestion >300,000 IU. Chronic toxicity (hypervitaminosis) associated with doses >10,000 IU/day. Symptoms of chronic hypervitaminosis A include skin desquamation, liver impairment, loss of vision and severe intracranial hypertension.

Vitamin B_3/niacin/nicotinic acid

Moderate to high doses of vitamin B_3 are commonly associated with peripheral vasodilation causing skin flushing, burning sensation, pruritus and hypotension. Vasodilation may also occur in the eye resulting in reversible toxic cystoid macular oedema.

Vitamin B_6/pyridoxine

Doses ≥200 mg/day of vitamin B_6 have been associated with severe sensory peripheral neuropathies. Risk often arises from multiple products being taken all containing pyridoxine.

Vitamin C/ascorbic acid

Associated with precipitation of cysteine, urate or oxalate kidney stones, especially in people with a predisposition for kidney stones. Vitamin C may reduce effectiveness of antineoplastic drugs such as vincristine, doxorubicin, methotrexate, cisplatin and imatinib.

Vitamin D/colecalciferol

Very high doses may cause hypercalcaemia, with symptoms from thirst and polyuria to seizures, coma and death. High intermittent doses of vitamin D have been associated with increased risk of falls and fracture in the elderly.

Vitamin E/alpha-tocopherol

Antiplatelet effect and increased risk of haemorrhagic stroke reported.

Calcium

Carbonate salt can cause gastric reflux and constipation. High-dose calcium may induce vascular and soft tissue calcification, hypercalciuria, kidney stones and secondary hypoparathyroidism. Interferes with absorption of magnesium, iron and zinc if taken simultaneously, and can reduce absorption of many other drugs e.g. levothyroxine, tetracyclines.

Magnesium

High doses often result in diarrhoea, nausea and abdominal cramping due to the osmotic effect. Like other divalent cations, magnesium may chelate and reduce absorption of other minerals or medicines such as tetracyclines.

Zinc

Often associated with altered or impaired taste and smell. Intranasal zinc can cause anosmia. Doses ≥80 mg/day in clinical trials were associated with adverse prostate effects.

Selenium

Associated with acute and chronic toxicity. Signs of chronic high-dose 'selenosis' are hair and nail loss or brittleness, lesions of the skin and nervous system, nausea, diarrhoea, skin rashes, mottled teeth, fatigue and mood irritability.

Box 2 Six potential harms of a supplement or medicine

Adverse effects

Adverse effects should be considered from short- or long-term use, high or low dose, risk during pregnancy or breastfeeding, influence on disease, fertility or malignancy.

Drug interactions

Drug–drug or drug–disease interactions, dynamic or kinetic.

Enzyme and transporter interactions, all of which can make other drugs more toxic or less effective.

Cost

The cost of dietary supplements can be harmful due to its impact on finances and the ability to afford treatment or other essential items.

Delay of more effective therapy

Time spent taking ineffective products may delay more effective interventions, waste valuable time and allow disease progression.

False hope or fraud

Falling for fraudulent claims offering false hope can be demoralising and depressing, which for some can make the difference between continuing to manage a health condition and giving up hope.

Medication burden

As the number of medicines and supplements increases, so too does the burden of polypharmacy which increases the risk of medication error, interactions and adverse events.

Adapted from reference 4

effective or safe dose. Indeed, overdose of ingredients from multiple products, such as pyridoxine or vitamin A, is a much-neglected risk.

For consumers to make balanced and informed decisions about using dietary supplements, details regarding both their benefits and harms should be evidence-based and readily available. Such information can be found, especially on the internet, but consumers have to be motivated to look, know where to look, and know how to critique the information. Health professionals can assist consumers by openly discussing the risks and benefits of dietary supplements, explain why dose is important, and direct them where to go for higher quality information beyond advertising and the manufacturer's label. See Box 3 for links to information resources freely available to both consumers and health professionals regarding dietary supplements and complementary medicines.

When taking a comprehensive history, health professionals should include dietary supplements, detailing the brand, its ingredients and the dose taken in order to assess both the potential benefits and risks, and the potential for cumulative overdose from multiple products. As with all medicines, adverse events associated with dietary supplements should be reported to the TGA ensuring brand names are specified so all ingredients can be identified.

Box 3 **Freely available resources regarding dietary supplements and complementary medicines**

About Herbs – Memorial Sloane Kettering Cancer Care Centre

http://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search

Drugs.com

www.drugs.com

National Institutes of Health, Office of Dietary Supplements

https://ods.od.nih.gov/HealthInformation/makingdecisions.sec.aspx

National Institutes of Health, National Center for Complementary and Integrative Health

www.nccih.nih.gov

Vitamin A

Vitamin A, also known as retinol, is associated with acute and chronic toxicity. Acute toxicity is mostly caused by accidental ingestion of 300,000 IU or more.[5] Signs and symptoms include headache, blurred vision, dizziness, nausea, vomiting and reduced motor coordination secondary to intracranial hypertension.[6]

Vitamin A toxicity can occur with regular ingestion of more than 100,000 IU daily, which may be contributed to by synthetic retinoids. Symptoms of chronic hypervitaminosis A include skin desquamation, liver impairment, loss of vision and severe intracranial hypertension.[6]

Vitamin A taken by pregnant women is associated with birth defects. Ingestion of high-dose vitamin A (>15,000 IU/day from combined sources of food and supplements or >10,000 IU/day from supplements only) has been associated with an increased incidence of craniofacial malformations as well as central nervous system, heart and limb abnormalities.[7]

Vitamin B_3

Moderate to high doses of vitamin B_3 (niacin/nicotinic acid) (500 mg/day or more) are commonly associated with peripheral vasodilatation causing skin flushing, burning sensation, generalised pruritus and hypotension, lasting for 20–30 minutes and declining in severity and frequency with time.[8] Niacin-induced vasodilatation also occurs in the eyes. This can result in reversible toxic cystoid macular oedema in 0.67% of patients taking doses of niacin 3–4.5 g daily.[9] Doses of 3 g or more of niacin per day have caused blurred vision, eyelid oedema, toxic amblyopia, proptosis, loss of eyelashes or eyebrows and superficial punctate keratitis.[10]

Vitamin B_6

Vitamin B_6 (pyridoxine) has been associated with severe sensory peripheral neuropathies most frequently in doses over 200 mg/day.[6] Because of this potential neurotoxicity, products containing pyridoxine with a daily dose more than 200 mg/day are Schedule 4 prescription-only medicines in Australia and overseas.[11]

Vitamin C

Urine acidification from supplemental vitamin C (ascorbic acid) in doses as low as 250 mg/day has been associated with precipitation of cysteine, urate or oxalate kidney stones, especially in men and people with a predisposition for kidney stones.[6,12-14] Vitamin C also has many well-known pharmacodynamic drug interactions. One of the more serious interactions is that it may reduce the effectiveness of antineoplastic drugs such as vincristine, doxorubicin, methotrexate, cisplatin and imatinib.[15]

Vitamin D

Vitamin D (colecalciferol) in doses of 1000–2000 IU/day is well tolerated. However, there are increasing reports of toxicity which appear to relate to manufacturing errors, prescribing errors and the increasing use of high-dose supplements. Toxicity is mediated through hypercalcaemia, with symptoms ranging from thirst and polyuria to seizures, coma and death.[16] High-dose vitamin D in the range of 300,000–500,000 IU administered as an annual intramuscular injection for osteoporosis has been associated with increased risk of fracture.[17,18] Doses of 4000–10,000 IU/day have been associated with diminished bone density.[19]

Vitamin E

Vitamin E has been associated with an antiplatelet effect and two clinical trials have found an increased risk of haemorrhagic stroke in people taking alpha-tocopherol.[20] Two meta-analyses of randomised trials have also raised questions about the safety of high-dose vitamin E in daily doses of 400 IU or more for over one year, which have linked supplementation with small but statistically significant increases in all-cause mortality.[6,21]

Calcium

Calcium supplementation, especially in the carbonate salt, can cause gastric reflux and constipation. High-dose calcium may induce vascular and soft

tissue calcification, hypercalciuria, kidney stones and secondary hypoparathryoidism.[22] Calcium also interferes with the absorption of magnesium, iron and zinc if taken simultaneously.[23]

Magnesium

Magnesium in high doses from dietary supplements or medicines often results in diarrhoea, nausea and abdominal cramping due to the osmotic effect of unabsorbed salts in the intestine.[24] The salts most likely to cause diarrhoea are magnesium carbonate, chloride, gluconate and oxide.[6] Symptoms of hypermagnesaemia usually develop when serum concentrations exceed 1.74–2.61 mmol/L and include hypotension, nausea, vomiting, facial flushing, urine retention, ileus, depression and lethargy. This may progress to muscle weakness, difficulty breathing, extreme hypotension, irregular heartbeat and cardiac arrest.[25]

Zinc

Zinc, even in small doses, is associated with adverse effects on taste and smell. Anosmia is associated with intranasal use.[6] Acute high-dose zinc (>40 mg/day) can cause nausea, vomiting, abdominal cramps, diarrhoea and headaches.[26] It is well established that long-term high-dose zinc can induce copper deficiency.[6] In the Age-Related Eye Disease study (AREDS), 80 mg/day of zinc oxide for an average of 6.3 years was associated with a significant increase in hospitalisations for genitourinary causes. This raises the possibility that chronic high-dose zinc adversely affects prostate health.[27]

Selenium

Selenium toxicity can occur with acute or chronic high-dose ingestion.[6] Early indicators of excess intake are 'garlic breath' and a metallic taste in the mouth. Signs of chronic high selenium intake or 'selenosis' are hair and nail loss or brittleness, lesions of the skin and nervous system, nausea, diarrhoea, skin rashes, mottled teeth, fatigue and mood irritability. Oral selenium products with a daily dose of 300 micrograms or more are regulated as Schedule 4 medicines because of their potential toxicity.[11]

Iron salts

Adverse effects of oral iron supplements are dose related, so a key predictor of harm is assessing how much elemental iron is being taken. Some commercial iron supplements only contain tiny doses, that is 10–20 mg iron per unit, which reduces the risk of adverse effects but also the chance of benefit.

Typical adverse effects of therapeutic iron doses, such as 100–200 mg/day include abdominal pain, nausea, vomiting, constipation, diarrhoea and black discolouration of faeces. Black discolouration of teeth is associated with liquid iron preparations.

Folic acid

Folic acid is well tolerated in fortified foods and supplemental doses used for medical indications up to 1 mg daily.[6] Doses from 5–15 mg/day have been associated with a range of gastrointestinal adverse effects including abdominal cramps, diarrhoea, nausea, flatulence and a bitter taste in the mouth.[6]

Due to its antagonistic effects, folic acid reduces the adverse effects of methotrexate used in management of rheumatoid arthritis. However, it may decrease the efficacy of methotrexate in the treatment of acute lymphoblastic leukemia[28] and psoriasis.[29] Excess folate or folic acid may mask vitamin B_{12} deficiency.[30]

Conclusion

Dietary supplements have a range of potential risks and few benefits. Consumers should be aware that there is no case for vitamin or other supplements in normal healthy people, who are not pregnant or breastfeeding and are consuming a healthy diet.[31]

In order to make informed decisions about dietary supplement use, consumers require information on both their benefits and harms. As the risks of dietary supplements are not well known, manufacturers should be required to make this information more readily available. Health professionals and consumers should report adverse events associated with dietary supplements to the TGA. <

Conflicts of interest: none declared

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